

ORIGINAL ARTICLE

The benefit of scratch patch testing to demonstrate ocular contact allergy to brimonidine tartrate

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Abstract

Introduction: Ocular allergies to brimonidine are frequent in patients treated for glaucoma. There is variability in reporting due to the lack of diagnostic criteria and the absence of cutaneous testing. Many false-negative patch tests (PT) have been described. Alternative methods, such as strip and scratch PT, have been used without a standardized method.

Objectives: The primary objective is to identify the best method of cutaneous testing and brimonidine concentration for patch testing. The secondary objective is to identify clinical signs and symptoms suggestive of ocular allergy.

Patients and Methods: A retrospective review of patient files suspected of brimonidine ocular allergy was performed. Patch testing method, brimonidine concentration and clinical symptoms were reviewed.

Results: Of the 36 patients identified, half tested positive for brimonidine for at least one of the testing methods. The scratch PT demonstrated 17 positive reactions (94% detection rate). Three patients reacted with strip PT. No positive results were found with standard PT. The 5% brimonidine concentration demonstrated the highest sensitivity. The absence of eyelid pruritus was associated with negative testing.

Conclusion: In the investigation of ocular allergy to brimonidine, scratch PT proved to be an essential tool. Brimonidine 5% pet. appeared as the most sensitive concentration for scratch PT.

KEYWORDS

allergic contact dermatitis, brimonidine, conjunctivitis, ocular allergy, ocular pruritus, patch test, scratch patch test, strip patch test

1 | INTRODUCTION

Brimonidine tartrate is a topical selective α_2 adrenergic agonist used alone or in combination with other molecules to lower intraocular pressure in patients suffering from glaucoma. Ocular allergies to brimonidine are a frequent side-effect of brimonidine treatment that commonly leads to therapy discontinuation.¹ Ocular allergy encompasses a range of clinical manifestations, including palpebral dermatitis and ocular manifestations such as tearing, redness, pruritus, burning, papillary hypertrophy and follicles.² Besides clear palpebral dermatitis,

some of these symptoms (e.g., conjunctivitis) are less specific but might still point to an underlying contact allergy, and thus justify the need to conduct an allergy work-up, including (modified) patch testing.

A definitive diagnosis of brimonidine allergy is difficult to confirm due to the number of concurrent potential offending agents as well as a large differential diagnosis for this condition. Patients treated for glaucoma often need a combination of topical agents to control their chronic disease. Choosing to discontinue a molecule for a possible allergy without confirmation may result in depriving the patient of an

important treatment option. In doubt, a proper allergy workup might help define the diagnosis.

The reported rate of ocular allergies to brimonidine ranges from 4.2% to 25.7%, according to various studies.^{3–5} There is also a large variability between the initiation of treatment and supposed brimonidine allergy in the literature with a mean time ranging from 6 to 9 months and a wide interval ranging from 14 days to 3 years.^{1,3,5} This significant variability could be due to the lack of validated diagnostic criteria as well as to the absence of cutaneous testing to confirm the allergy.

Many false-negative patch tests (PT) for topical ophthalmic molecules have been described in the literature.⁶ The repeat open application test (ROAT) is one alternative method that has been used to investigate ocular allergies.⁷ Although recognized to be a reliable test, this method is challenging to implement for some patients, especially elderly patients with low vision due to glaucoma. Indeed, when investigating for potential allergies to more than one molecule and preservatives, this method becomes rapidly overwhelming. Compliance by patients as well as adequate adherence to the procedure are factors to consider when using the ROAT. Alternative testing methods, such as strip and scratch PT may be less demanding for patients and have been used successfully in the diagnosis of allergic contact dermatitis from ocular medications.⁸ However, there is yet no accepted standardized method to investigate ocular allergies.⁷

2 | OBJECTIVES

The primary objectives of this study are to identify the best method of cutaneous testing when investigating ocular allergy to brimonidine as well as to identify the optimal concentration of brimonidine that should be used for cutaneous testing. The secondary objective of this study is to determine clinical signs and symptoms most suggestive of ocular contact allergy to brimonidine.

3 | PATIENTS AND METHODS

After approval by our institution's research ethics board, we retrospectively reviewed files from patients suspected of brimonidine ocular allergy who had undergone cutaneous testing in our specialized contact dermatitis centre between 1 July 2017 and 30 June 2019. Data on sex, age, history of atopy, clinical presentation and test results were collected from medical records.

Patch testing was performed using pure brimonidine tartrate (Gentès et Bolduc) diluted in pet. at different concentrations (0.1%, 0.33%, 1%, 5%) by our hospital pharmacy. When available, patients' ophthalmic drops were also tested (0.2%). Most patients were tested with a customized glaucoma series which included benzalkonium chloride 0.1% aq., ethylenediaminetetraacetic acid disodium salt dihydrate 1.0% pet. both obtained from Chemotechnique Diagnostics as well as commercialized glaucoma medications available in Canada ('as is'), namely, those containing timolol maleate 0.5% aq., levobunolol 0.5%



FIGURE 1 Scratch patch test (PT) technique and layout. Standard PT and strip PT performed side by side and scratch patch test consisting of the technique described in Table 1

TABLE 1 Scratch patch test (PT) method

1. Application of haptens in the chambers (in duplicate patches) immediately prior to putting the patches on the patient.
2. Installation of the first set of chemicals (first patch) on the back of the patient.
3. Use of an alcohol swab to clean the patient's back approximately where the scratch PT will be applied. Leave it to dry completely.
4. Using the first set of patches as a guide, use of a 30-gauge needle for scarification of the skin in a parallel straight diagonal pattern, on each site where chemicals will be applied. The pressure needs to be sufficient to cleave the stratum corneum without drawing blood.

aq., betaxolol 0.5% aq., brinzolamide 1% aq., dorzolamide 2% aq., apraclonidine 1% aq., bimatoprost 0.01% aq., latanoprost 0.005% aq., travoprost 0.003% aq. and pilocarpine 2% aq.

All haptens were tested with three different techniques: PT, strip PT and scratch PT. Strip PT consisted of 10 repeated applications of adhesive tape (Transpore Surgical Tape; 3M) on the skin before patch placement. Scratch PT consisted of scarification of the epidermis before patch placement (Figure 1). The detailed method is described in Table 1. ROATs were not performed.

All haptens were mounted on IQ chambers and applied to the patient's back and/or upper external arms on unaltered skin, after tape stripping and on scarified skin on Day 0. The patient was asked to keep his/her back or arms dry until the final reading. On Day 2, the patches were removed and the first reading was obtained. The final

TABLE 2 Distribution of positive tests to brimonidine, by concentration and type of testing

	Standard PT	Strip PT	Scratch PT
Own Rx	0	0	4 (22%)
0.1%	0	1 (6%)	6 (33%)
0.33%	0	0	4 (22%)
1%	0	0	7 (39%)
5%	0	2 (11%)	16 (88%)
Total	0	3 (17%)	17 (94%)

Abbreviations: Rx, drugs; PT, patch test.

reading was performed on Day 4. The readings were scored according to the International Contact Dermatitis Research Group standards. A reaction was considered positive if rated + or above.

Twenty control patients were also tested with the different brimonidine concentrations using PT, strip PT and scratch PT. Controls were consecutive 'non-exposed' patients randomly selected among dermatitis patients referred for patch testing, without known exposure to brimonidine. Out of 36 patients, 19 also served as internal controls. In those patients, the complete glaucoma series was performed, also with scratch PT, although they had not been exposed to all the molecules tested. Results are discussed below.

3.1 | Statistical analyses

Quantitative variables are described as mean $\pm$ standard deviation or median and interquartile range for non-normal variables. Qualitative variables were presented as frequencies and percentages. The χ^2 or Fisher exact tests were used for categorical data comparisons when appropriate. Continuous variables were tested using the Wilcoxon-Mann-Whitney test after normality verification. The sensitivity and specificity were estimated with exact (Clopper-Pearson) confidence limits. The superiority Clopper-Pearson exact tests were applied to evaluate whether sensitivity or specificity exceeded 50% with a superiority margin of 5%. Statistical analyses were performed using SAS Statistical Software v.9.4 (SAS Institute) with a two-sided significance level set at $p < 0.05$.

4 | RESULTS

Between 1 July 2017 and 30 June 2019, 36 patients were tested for suspicion of ocular allergy to brimonidine. The male:female ratio was 0.9:1. The mean age of the patients was 69.8 ± 9.9 years (ranging from 46 to 94) with a median of 70.0 years. Seven patients (19%) had a personal history of atopy. The onset of symptoms after brimonidine initiation in the positive group ranged between 1 week and 5 years (mean 62 weeks, median 9 weeks). In comparison, the negative test group, that is, patients that were evaluated for a possible brimonidine contact allergy but in whom PT and alternative test methods came

TABLE 3 Scratch PT results

Scratch	–	?/+	+	++	+++
0.1%	29	2	5	0	0
0.33%	24	8	4	0	0
1%	23	6	5	2	0
5%	20	0	10	5	1

Abbreviation: PT, patch test.

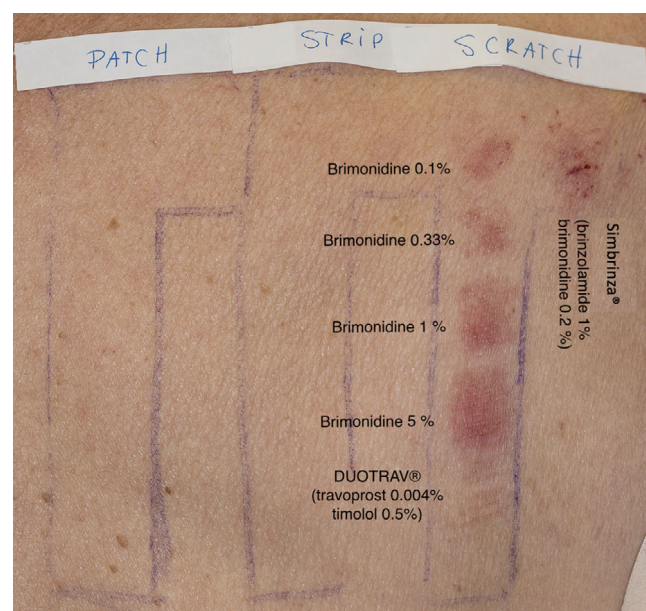


FIGURE 2 Results at Day (D) 4 of standard patch test (PT), strip PT and scratch PT test. There is an increasing reaction to brimonidine from 0.1% to 5% and a ++ reaction to the own brimonidine-containing ophthalmic preparation (Simbrinza); negative reaction to another ophthalmic drug (Duotrav)

back negative, ranged between 0.3 weeks and 10 years (mean 89 weeks, median 38 weeks) demonstrating a large variability ($p = 0.76$). Complete patient characteristics and clinical findings are available in the Supporting Information Material (Table S2).

Among the 36 patients included in the study, 50% (18 of 36 patients) were positive for brimonidine for at least one of the PT methods. No positive result was found with standard PT. Three patients (8%) reacted positively with strip PT. Scratch PT detected 94% (17/18 patients) of the positive reactions, and one patient reacted only to the strip PT 0.1% (Table 2).

Scratch PT demonstrated positive reactions in a concentration-dependent manner, the 5% brimonidine concentration being the most sensitive. Concentrations of 1% and lower demonstrated milder or doubtful reactions, while the 5% concentration demonstrated stronger reactions (Table 3 and Figure 2). Detailed PT results are available in the Supporting Information Material (Table S3).

Assuming that all allergies were detected with our investigations and that no reaction was a false positive, scratch PT with brimonidine

TABLE 4 Sensitivity analysis

Scratch PT brimonidine	Number of patients with negative tests (– or ?/+)	Number of patients with positive tests (+, ++ or +++)	Sensitivity	p Value (H ₀ : Sensitivity-50% ≤ 5%)
0.1%	31	5 (14%)	28%	0.9951
0.33%	32	4 (11%)	22%	0.9990
1.0%	29	7 (19%)	39%	0.9463
5.0%	20	16 (44%)	89%	0.0025

Abbreviation: PT, patch test.

5% had a sensitivity of 89% ($p = 0.0025$). The specificity of the test was 100% for all concentrations. (Table 4).

The absence of eyelid pruritus was associated with negative testing. Indeed, all but one patient (93%) with negative testing reported no pruritus. Only one patient (7%) with positive testing reported no pruritus ($p < 0.0001$). On the other hand, 81% (17 of 21 patients) of patients reporting eyelid pruritus had positive tests. Pruritus, therefore, seemed to be a marker of ocular allergy.

Of note, the presence of conjunctival follicles on ophthalmic examination did not correlate significantly with brimonidine ocular allergy ($p = 0.4430$). They were present in 66% (12 of 18 patients) of the negative PT patients and 83% (15 of 18 patients) of the positive PT patients.

All 20 non-exposed control patients were negative to (all concentrations of) brimonidine on PT, strip PT and scratch PT.

The glaucoma series (including benzalkonium chloride) was tested in 19 of 36 patients. Benzalkonium chloride alone was tested in five patients not tested in the glaucoma series. Only one of the 24 patients tested with benzalkonium chloride demonstrated a doubtful reaction (?/+), potentially irritant (IR) in nature, to this preservative on scratch PT. Three patients tested positive for other ophthalmic medications (pilocarpine, timolol and brinzolamide–timolol combination) on scratch PT. All those reactions were considered clinically relevant. Therefore, 24 patients served as internal controls, tested with benzalkonium chloride, with only one patient showing a doubtful reaction, judged to be an irritant reaction. Nineteen patients served as internal controls tested with the glaucoma series and tested negative for other molecules except for three cases of clinically relevant allergies.

Seventeen patients were tested with their ophthalmic medications. Four of them tested positive for their medication containing brimonidine (either brinzolamide/brimonidine tartrate 1%/0.2% wt/wt or brimonidine tartrate/timolol maleate 0.2%/0.5%), on scratch PT, all of them also being positive to brimonidine dilutions. None of the patients reacted to their ophthalmic medication with the standard PT or strip PT techniques.

The final diagnosis in patients with negative brimonidine testing included irritant contact dermatitis, allergic contact dermatitis to another medication, ocular rosacea or dermatconjunctivitis of unknown cause. Of the 18 patients with suspected allergy to brimonidine but with negative test results, 4 patients had successfully re-introduced brimonidine in their current treatment (Table S1). One patient was lost to follow-up, and the remaining patients did not re-

introduce brimonidine as a treatment for their glaucoma. The reason for not reintroducing brimonidine despite negative testing varied: 2 patients had surgical treatment, 7 patients had laser treatment(s) and 12 patients necessitated multiple-drop therapies to control the disease. Fear of symptom recurrence by the patient and/or the treating ophthalmologist was also a factor that contributed to this decision.

5 | DISCUSSION

It is thought that weakly sensitized individuals might clinically react to their ophthalmic medications but not on patch testing on the back because the antigens might not be potent enough and/or might not easily penetrate the skin stratum corneum of the back to induce an allergic reaction. Epidermal manipulation before patch testing is used to enhance antigen penetration. Different manipulation methods have demonstrated their utility in various situations including when testing ocular medications, namely, scratch PT^{9–15} and strip PT.^{16–18} Consistent with those previous reports, standard PT was of no utility for our patients.

In our study, scratch PT detected the vast majority of positive reactions (94%) while strip PT was of low additional value. This could be explained by the fact that strip PT removes only the top layers of the stratum corneum, while scratch PT breaches the whole stratum corneum layer, if not the whole epidermis. It is thus logical that scratch PT is more efficacious at enhancing antigen penetration than strip PT.

The validity and possible irritancy of scratch PT is often brought into question, although its reproducibility has been established for many years.¹⁹ The detailed description of our technique (Table 1) highlights the simplicity and usability of this method in clinical practice. In our patients, the gradient of positivity observed with different brimonidine concentrations as well as the negative controls suggest that the positive scratch PT represented true allergic reactions. Although irritant reactions to the scratch PT technique are probably more common than to the traditional PT due to its inherent disruption of the corneal layer, this was not found to be the case in our patient population. Indeed, of the 24 patients tested with benzalkonium chloride, a known irritant, only one patient showed a doubtful (?/+) reaction to the scratch PT. Also, 19 of 36 index patients were scratch patch tested to a range of molecules they had not been exposed to

(glaucoma series) and 20 'non-exposed' controls were scratch patch tested to the brimonidine dilutions with no irritant reaction. Consequently, our findings suggest that the scratch PT technique might be less irritant than previously assumed and that it could be considered more often in the investigation of eyedrops allergy, as well as in other settings, such as in the investigation of drug allergies.

In our study population, brimonidine was successfully re-introduced in 4 of 18 patients that were tested negative. The other patients had been treated with a combination of other molecules, laser and/or surgery. Unfortunately, not all patients are candidates for surgical treatment, and multiple-drop therapies have been shown to yield shorter-lasting benefits as well as were associated with an increased clinical and economic burden for the patient.¹ The principle that 'symptoms of allergy' necessitate changing of medication has been in place for many years in the ophthalmology community. Such an established practice is challenging to modify, as this is reflected in our population. We postulate that by systematically investigating potential ocular contact allergy to brimonidine, by proving true allergies with positive testing and by offering other potential diagnoses to patients with negative testing, one may ultimately change the established practice, to the benefit of the patients.

To our knowledge, brimonidine cutaneous testing for ocular sensitization has only been investigated in a single other reports in two patients that were described as having a positive PT to brimonidine ophthalmologic preparations without additional details.²⁰ Concerning brimonidine specific testing, in a recent review published by Grey et al. on patch testing for topical ophthalmic medications, no specific concentration was established for brimonidine testing.⁷ In addition, cutaneous brimonidine sensitization when used to treat rosacea has been described frequently but only demonstrated by PT in four case reports.^{21–24}

Also consistent with previous reports, our findings demonstrated a high rate of false-negative reactions to patients' ophthalmic medications. We believe this may be partly due to the low brimonidine concentration in those medications, which contain either 0.15% or 0.2% of the active ingredient. This correlates well with our results which showed that brimonidine 0.1% or 0.33% combined would have detected the allergy in only six (33%) of our patients. Another possible explanation might be that the vehicle used in ophthalmic preparations is less efficient to penetrate the epidermis. Therefore, it is important to remember that scratch patch testing ophthalmic drugs 'as is' may still rather frequently result in false-negative reactions, whereas scratch patch testing the active ingredients, such as brimonidine, in a higher concentration is useful to detect an ocular allergy.

Ocular allergy to brimonidine is frequently encountered in ophthalmology practices. It is diagnosed according to clinical signs and symptoms. Patients presenting with itching, discomfort on instillation, eyelid dermatitis or conjunctival hyperemia with papillary and/or follicular conjunctival reaction on slit-lamp evaluation are considered to have ocular allergies.² However, those signs and symptoms could also be due to other diagnoses including blepharoconjunctivitis and follicular conjunctivitis of other aetiology (viral, chlamydial, toxic, associated with molluscum contagiosum, etc.).

Our findings suggest that the absence of pruritus should lead the clinician to search for causes other than brimonidine allergy. The significance of this result remains limited, pruritus being a subjective finding that was recorded based on patients' memory of their symptoms or from medical records. Conjunctival follicles, assumed to be a reliable marker of ocular allergy in previous studies⁵ did not seem to correlate with positive testing in our study. However, most patients referred for testing demonstrated follicles on ocular examination while exposed to brimonidine.

Consequently, we suspect that many cases of alleged ocular allergy to brimonidine may be misdiagnosed because of the lack of reliable cutaneous testing capable of confirming the allergy. By having a valid test method to differentiate between true allergy to brimonidine and non-specific inflammation due to other causes, an important treatment option for glaucoma could potentially be re-introduced.

6 | LIMITATIONS

The first limitation of our study concerns its retrospective nature. Not all patients were tested with their ophthalmic medications as patients often forgot to bring their eyedrops, preventing their testing. The glaucoma series was also put into place later, resulting in early date patients not being tested with these additional haptens, which included their eyedrops 'as is'. Therefore, we may have underestimated the value of testing patients' medication. More specifically, 13 patients were referred for testing in the context of treatment with Simbrinza, a combination of brimonidine and brinzolamide. Brinzolamide tested negatively in 10 of 13 patients and was not tested in 3 of 13 patients. Of the three patients not tested for brinzolamide, one had a positive reaction to brimonidine and two tested negatively to it. Nine patients were referred for testing in the context of treatment with Combigan, a combination of brimonidine and timolol. Timolol was tested in six of those nine patients, with one patient showing positive reactions to both timolol and brimonidine. Of the three patients not tested for timolol, two had a positive reaction to brimonidine and one tested negatively to it.

A second potential limitation relates to the test concentrations used. Testing to higher concentrations of brimonidine, for example, starting at 10%, with serial dilutions at 1%, 0.1%, 0.01% and 0.001%, might have been useful to observe a clearer gradient of positivity and to potentially increase the sensitivity with the higher concentration (i.e., 10%). Adding a late PT reading on D7 and later might also have increased the positivity rate. The additional use of the ROAT test might have proven useful to confirm positive reactions. More importantly, negative ROAT could have confirmed the absence of brimonidine allergy in patients with negative testing but for whom brimonidine was not re-introduced.

A third potential limitation can be attributed to the product manufacturing and the test technique in itself. Some variability in scratch PT results have been noted in three patients, with lower concentration giving positive or stronger results than higher

concentration tested. This variability may be consistent with the inherent variability of patch testing, possibly due to the quantity of allergen applied as well as to slight differences in the scratching performed.

Finally, the number of patients in our study remains small to assess clinical significance but points towards scratch PT being a more sensitive method of testing for ophthalmic medications.

7 | CONCLUSION

Our results provide important insights about cutaneous testing for suspected ocular allergies to brimonidine tartrate. Scratch PT proved to be an essential tool in this context. Brimonidine 5% pet. appeared as the most sensitive concentration for scratch PT. More patients need to be investigated to confirm our findings as well as to be able to correlate clinical signs and symptoms with positive testing. Nevertheless, we strongly suggest using scratch PT when investigating ocular medication allergies.

The findings of this study also suggest that the scratch PT technique might be less irritant than previously stated. Consequently, it could be considered more often in the investigation of other ophthalmic drugs, as well as in the investigation of other drug allergies (e.g., with regard to large molecules that do not easily penetrate the skin).²⁵

AUTHOR CONTRIBUTIONS

Julien Ringuet: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); writing – original draft (lead).

Caroline Lajoie: Investigation (supporting); validation (supporting); writing – original draft (supporting). **Serge Bourgault:** Validation (supporting); writing – original draft (supporting). **David Simonyan:** Data curation (equal); formal analysis (equal); validation (equal); writing – original draft (equal). **Marie-Claude Houle:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (lead); supervision (lead); validation (lead); writing – original draft (equal).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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